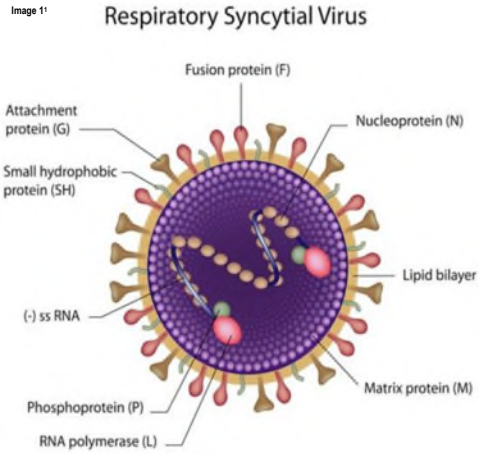
CONNECTICUT MEDICAL ASSISTANCE PROGRAM
DEPARTMENT OF SOCIAL SERVICES
&
ACENTRA HEALTH
QUARTERLY NEWSLETTER

Protection Against Infection—What You Need to Know about Respiratory Syncytial Virus (RSV)

Respiratory Syncytial Virus (RSV) was first isolated from chimpanzees in 1955. The following year it was found to infect people and identified as a human threat. RSV is a single strand RNA virus encapsulated in a lipid bilayer adorned with a handful of transmembrane glycoproteins (Image 1).[1] Two transmembrane glycoproteins are of note. Attachment transmembrane glycoprotein (G) binds the virus to host respiratory epithelial cells while fusion transmembrane glycoprotein (F) fuses the virus to the epithelial cells allowing for viral penetration into the host cell, ensuring replication will commence.[2,3] A combination of the immune response elicited from host cell infection and viral toxicity causes respiratory epithelial cell death which leads to a buildup of cellular debris, mucous production, airway obstruction, and edema within the lungs.

Image 1[1]



The RSV virus is categorized into two subtypes, RSV-A and RSV-B and is typically spread by aerosolized droplets or by contact with contaminated surfaces. Infected patients are contagious for 3-8 days and present with symptoms such as rhinorrhea, pharyngitis, sneezing, cough, headache, fatigue, and fever.[4] While most patients experience upper respiratory infections, RSV can cause more serious lower respiratory tract infections (LRTIs) such as bronchiolitis or pneumonia, especially in infants and patients older than 65 years of age with certain risk factors (Image 2)[4,5,6]. RSV follows a seasonal pattern typically beginning in October, peaking in December, and ending in April, however, in warmer climates this pattern may deviate from the norm. The COVID-19 pandemic impacted RSV infection rates and seasonality.[7] Reduced transmission of the virus during 2020, likely due to masking and widespread closures, rebounded during the following seasons (2021-2022 and 2022-2023) causing an increase in both the number of infections and severity of cases. This placed a significant burden on the healthcare system.[7,8]

On an annual basis, RSV is responsible for more than 30 million LRTIs, 3 million hospitalizations, and 100,000 deaths globally.[9,10] While the vast majority of infections and death occur in middle and low income countries, RSV is the leading cause of hospitalization in infants in the US.[5,9,11] 58,000-80,000 hospitalizations occur annually in US pediatric patients under the age of five.[3,12] Most children will have been infected with RSV by the age of two, however, infection does not provide long term immunity and reinfection is common.[5] As with many respiratory viruses, the very young and the very old are disproportionately affected. 60,000-160,000 hospitalizations and 6,000 – 10,000 RSV associated deaths occur annually in US patients > 65 years of age.[7,13] A recent study found that while RSV associated hospitalizations among older patients were less common than COVID-19 or influenza hospitalizations, clinical outcomes associated with RSV hospitalization were worse.[13]

Treatment of RSV consists of supportive measures only such as hydration, antipyretics, oxygen therapy, and mechanical ventilation. Ribavirin, administered via inhalation of aerosolized particles, is FDA approved to treat RSV infection, however, lack of efficacy and concern over toxicity deters use.[5] Due to the risk of severe illness and lack of treatment options, prophylaxis is the cornerstone of combatting this virus. Creating active immunity and passive immunity are two pathways to prevent RSV (Image 3).[14] Vaccination or infection with the virus illicit an active immune response, producing endogenous RSV antibodies and RSV distinct T cells.[15] Monoclonal antibodies (mAbs) and maternal vaccination create passive immunity by providing exogenous antibodies to infants who cannot produce their own.[15]

The first RSV vaccine, an inactivated whole virus vaccine, was developed in the 1960's. However, during safety testing, 80% of vaccinated children were hospitalized and two children died.[3,16] Further inquiry showed that

Image 2[4,5,6]

Risk factors for severe disease in infants[5]

- Premature birth
- Bronchopulmonary Dysplasia (BPD)
- Congenital Heart Disease (CHD)
- Immunocompromised
- Cystic Fibrosis
- Down Syndrome
- Age less than 6 months at time of infection
- Low birth weight
- Low socioeconomic status, low and middle income countries
- Simultaneous infection with another virus

Risk factors for severe disease in adults:[4]

- Pulmonary disease (asthma, COPD)
- CVD (cardiovascular disease)
- Diabetes
- Neurological disorders
- Renal or hepatic impairment
- Hematologic disorders
- Immunocompromised

Other risk factors that may contribute to severe disease to consider:[4]

- Frailty*
- Advanced age
- Resident of a long term care or nursing home

"*Frailty is a multidimensional geriatric syndrome and reflects a state of increased vulnerability to adverse health outcomes. Although there is no consensus definition, one frequently used tool is the Fried frailty phenotype in which frailty is defined as a clinical syndrome with three or more of the following signs or symptoms: unintentional weight loss (10 lbs [4.5 kg] in the past year), self-reported exhaustion, weakness (grip strength), slow walking speed, and low physical activity."[6]

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seronegative patients developed vaccine-associated enhanced disease (VAED) upon viral exposure post vaccination. This was caused by production of ineffective antibodies against the virus which escalated the host immune inflammatory response.[17] This halted progression of vaccine development for decades. Recently, however, scientists developed two vaccines that induce an immune response against RSVpreF, or pre-fusion transmembrane glycoprotein, targeting the pre-F form of the viral fusion protein, ultimately obstructing fusion of the virus to human respiratory epithelial cells and blocking viral penetration into the host cell.[18]

Arexvy, the first FDA approved RSV vaccine received approval in May 2023 for use in patients 60 years of age or older for the prevention of RSV disease.[19] This vaccine induces an immune response against RSVpreF3, or RSV pre-fusion 3 transmembrane glycoprotein, to protect against RSV associated LRTD.[5,19] Currently, a single intramuscular dose of the vaccine is recommended, 120 µg/0.5 ml after reconstitution, with ongoing studies to determine if subsequent doses will be needed.[4] One dose contains RSV-A subtype only and reduces RSV associated LRTD by approximately 83% during the 1st season and 56% during the 2nd season.[4]

Abrysvo, a second RSV vaccine, received FDA approval in July 2023. Similar to Arexvy, Abrysvo induces an immune response against RSVpreF, to protect against RSV associated LRTD.[20] While Abrysvo is approved to provide active immunization in individuals 60 years of age and older, it is also approved for use in pregnant women at 32 through 36 weeks gestational age for the prevention of RSV in infants from birth through 6 months of age.[5,20] Abrysvo induces a passive immune response in infants whose mothers receive vaccination, via maternal antibodies passed across the placental barrier to the fetus. Abrysvo was tested in pregnant women < 32 weeks gestation, however, there were more preterm births in vaccinated mothers (24-32 weeks gestation) versus non vaccinated mothers. While not statistically significant, the FDA determined that vaccination should only occur between 32 and 36 weeks gestation.[20] Pregnant women often receive vaccination with tetanus, diphtheria, and pertussis (Tdap). While Tdap and RSV vaccinations can be administered together, studies show that immune response to the pertussis component may not be as robust when given at the same time as Abrysvo.[15] Infants whose mothers receive vaccination with Abrysvo are typically protected if they are born at least 14 days after maternal vaccination and should not need additional prophylaxis with MAbs.[15] For both pregnant mothers and patients > 60 years of age, current recommendations call for a single intramuscular dose of the vaccine, 120 µg/0.5 ml after reconstitution, with ongoing studies to determine if subsequent doses will be needed.[4] A single dose contains 60 µg from RSV-A and 60 µg from RSV-B and is slightly more efficacious than Arexvy, reducing RSV associated LRTD by approximately 89% during the 1st season and 77% during the 2nd season.[4]

Both Arexvy and Abrysvo should not be administered to patients who are sick.[19,20] Common side effects of both vaccines include injection site pain, fatigue, myalgia, headache, and arthralgia.[19,20] A small number of patients in clinical trials for both vaccines developed atrial fibrillation after vaccination, however, the number was not sufficient to link causation to the vaccines.[6] 3 patients out of 17,922 vaccinated with Arexvy and another 3 patients out of 20,255 vaccinated with Abrysvo experienced inflammatory neurological events such as Guillain-Barré syndrome (GBS), chronic inflammatory demyelinating polyneuropathy, or acute central nervous system inflammation within 42 days after vaccination.[6] It was not determined if the neurological occurrences were associated with RSV vaccination. The Advisory Committee on Immunization Practices (ACIP) warned that coadministration of the RSV vaccine with other vaccines could potentiate adverse reactions.[6] Although both vaccines were effective in the prevention of RSV associated LRTD, studies were not powered to show efficacy regarding outcomes on hospitalization and death. However, vaccines do prevent RSV associated LRTD, therefore, likely prevent hospitalization and death.[6]

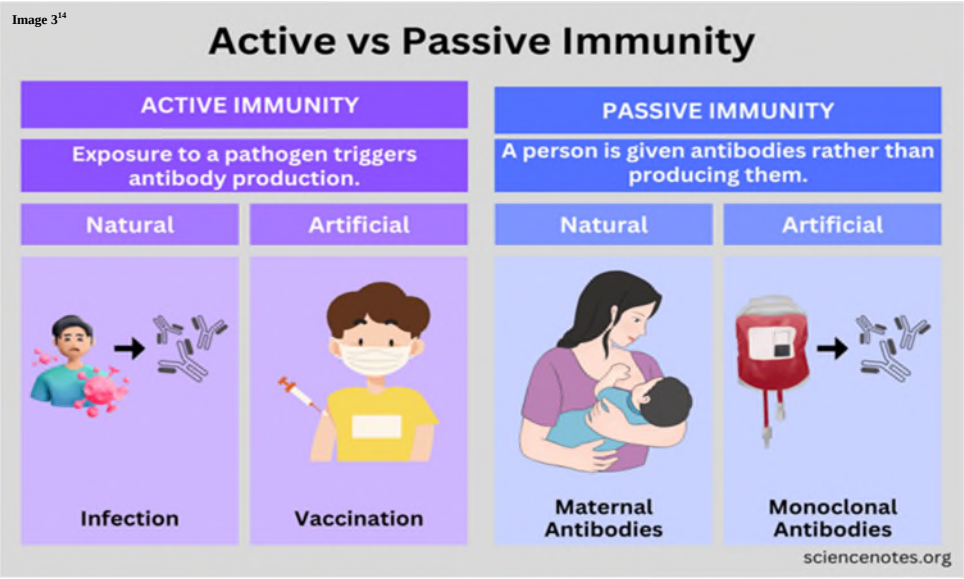
When determining whether a patient ≥ 60 years of age should receive vaccination, ACIP and the CDC recommend a single dose of either vaccine may be given using shared clinical decision making (SCDM).[21] RSV vaccination is not recommended across the board for all patients ≥ 60 years of age, rather the decision to vaccinate using SCDM should be made between patient and health care provider, taking into consideration individual patient characteristics, values, and preferences.[4]

Until a pediatric RSV vaccine is developed two options are available to prevent RSV infection in infants and children, both of which provide passive immunity. The first option, previously discussed, is the vaccination of pregnant women passing RSV antibodies to their fetus. The second option is direct treatment of the infant with MAbs.[15]

Palivizumab (Synagis) is a humanized monoclonal antibody that has been used since the late 1990's to prevent RSV in infants who are at high risk for severe infection. Palivizumab produces a short-term passive immunity by blocking RSV entry into host cells via the F protein which prevents RSV associated LRTI. Palivizumab is FDA approved for use in pediatric patients:[22]

- ♦ With a history of premature birth (less than or equal to 35 weeks gestational age) and who are 6 months of age or younger at the beginning of RSV season

Image 3[14]



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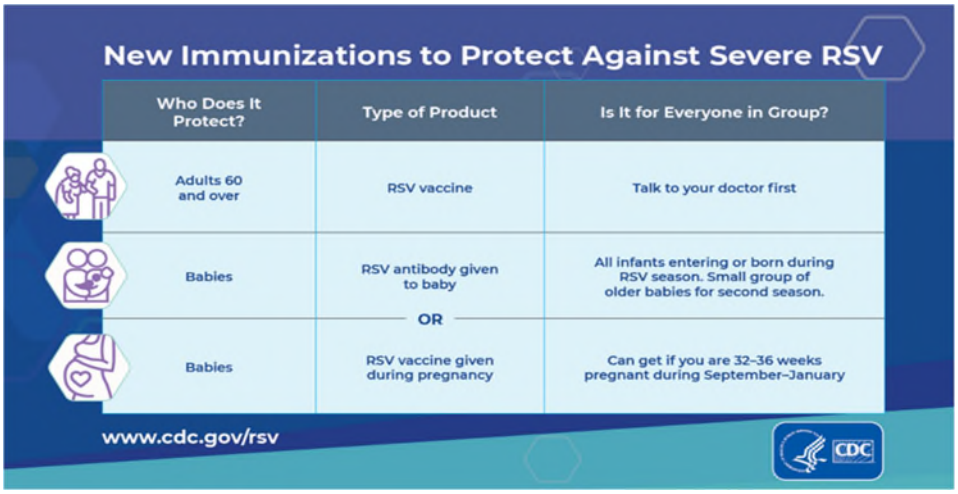
- With bronchopulmonary dysplasia (BPD) that required medical treatment within the previous 6 months and who are 24 months of age or younger at the beginning of RSV season
- With hemodynamically significant congenital heart disease (CHD) and who are 24 months of age or younger at the beginning of RSV season.

It is recommended that palivizumab be administered intramuscularly (15 mg/kg) once prior to the start of the RSV season and monthly thereafter, for up to 5 doses (months) per season.[22] Studies show that palivizumab reduces RSV hospitalization in high risk infants by up to 55%, however only about 5% of infants meet guidelines for use.[11,22] Palivizumab is expensive, ranging from $1,700 - $12,500 per infant per RSV season.[3,11] Due to the strict guidelines for use and high cost, this medication is only available to a small portion of those who may benefit from prevention of RSV.

Nirsevimab (Beyfortus) is a monoclonal antibody and an F protein inhibitor that recently received FDA approval during the summer of 2023. Like palivizumab it is indicated for the prevention of RSV LRTI, however, it is not restricted to use in high-risk infants only. Nirsevimab is indicated for all infants born during or entering their first RSV season and in children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season.[23] Nirsevimab has a longer ½ life compared to palivizumab with a single dose lasting for the entire RSV season and providing waning coverage into the 2nd season.[3] Studies show that nirsevimab reduces medically attended LRTI in infants by up to 79% and reduces hospitalization due to severe LRTI by 80%.[4,23] Due to its longer ½ life and availability to all infants, nirsevimab will likely take the place of palivizumab for use in infants and children to create passive immunity against RSV.

Based on CDC guidelines, nirsevimab is recommended for:[4]

- Infants under 8 months old born during – or entering – their first RSV season (typically fall through spring) if their mother did not receive an RSV vaccine, it is unknown if their mother received an RSV vaccine, or the mother received a vaccine but the infant was born <14 days after vaccination
- Nirsevimab can be considered in rare circumstances even though the mother received an RSV vaccine when, per the clinical judgment of the healthcare provider, the potential incremental benefit of administration is warranted:
  - Pregnant people who may not mount an adequate immune response to vaccination (e.g., people with immunocompromising conditions) or have conditions associated with reduced transplacental antibody transfer (e.g., people living with HIV infection)
  - Infants who have had cardiopulmonary bypass leading to loss of RSV antibodies
  - Infants with substantially increased risk for severe RSV disease (e.g., hemodynamically significant congenital heart disease, intensive care admission, and requiring oxygen at discharge)
- Some children between the ages of 8 and 19 months who are at increased risk of severe RSV disease before their second RSV season. These include:
  - Children who have chronic lung disease of prematurity who required medical support (chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen) any time during the 6-month period before the start of the second RSV season
  - Children with severe immunocompromise
  - Children with cystic fibrosis who have severe disease
  - American Indian and Alaska Native children



Nirsevimab is administered prior to the start of the RSV season (typically before October) as an IM injection, preferably in the upper thigh. It is not recommended for administration to children who are sick and caution is advised in infants with bleeding disorders.[23] Infants who are born during the RSV season should receive nirsevimab within 1 week of their birth if no maternal vaccine was received prior to birth.[21] Nirsevimab must be refrigerated and is available as a prefilled one time use syringe: 50 mg/0.5ml and 100 mg/ml.[23] 50 mg is the recommended dose for infants weighing < 5kg and 100 mg is the recommended dose for infants weighing ≥ 5 kg. The recommended dose for children entering their 2nd RSV season who are at an increased risk for severe disease is 200 mg. This medication is strictly intended for infants and children < 24 months of age.[23] Nirsevimab is less expensive compared to palivizumab at $495 per dose for 50 mg and 100 mg doses.[24] Due to the accessibility for all infants and lower cost, many will benefit from nirsevimab.

RSV is a common respiratory illness that can have devastating effects on vulnerable populations. It is the leading cause of hospitalization in infants in the US and causes thousands of hospitalizations and deaths in our older population. In infants, RSV LRTIs may contribute to the development of asthma and in older patients can exacerbate underlying disease states and contribute to additional health complications.[3,12] Due to a lack of immune stimulation during the pandemic, there was a rebound of the number and severity of viral infections after protective measures were lifted.[25] This places a significant weight on our healthcare system.[8] Utilization of new vaccines to create active immunity and use of MAbs to create passive immunity are tools we have to combat this illness, protect our population, and relieve added pressure on the healthcare system.

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